Lack of pharmacokinetic interaction between ropinirole and theophylline in patients with Parkinson’s disease

Abstract Objective: Ropinirole and theophylline have the potential to interact, because they use the same hepatic cytochrome P450 (CYP1A2) as their major metabolic pathway. The present study investigated the effect of steady-state oral theophylline on the pharmacokinetics of ropinirole at steady state and the effect of steady-state ropinirole on the pharmacokinetics of a single intravenous (i.v.) dose of theophylline, both in patients with idiopathic Parkinson’s disease (PD).

Methods: Pharmacokinetic parameters (AUC and Cmax) for i.v. theophylline were compared before and after a 4-week period of oral treatment with ropinirole (2 mg t.i.d.) in 12 patients with PD. Patients were then maintained at this dose of ropinirole, and oral theophylline was co-administered at doses of up to 300 mg b.i.d. The parameters AUC, Cmax and tmax for ropinirole were compared before, during and after oral theophylline co-treatment.

Results: Co-administration of ropinirole did not significantly change the pharmacokinetics of i.v. theophylline (mean AUC with and without ropinirole: 68.6 µg·h⁻¹·ml⁻¹ and 70.0 µg·h⁻¹·ml⁻¹, respectively; mean Cmax with and without ropinirole: 11.07 µg·ml⁻¹ and 11.83 µg·ml⁻¹, respectively). Similarly, there were no significant changes in ropinirole pharmacokinetics when the drug was co-administered with oral theophylline (mean AUC for ropinirole with and without theophylline: 21.91 ng·h⁻¹·ml⁻¹ and 22.09 ng·h⁻¹·ml⁻¹, respectively; mean Cmax for ropinirole with and without theophylline: 5.65 ng·ml⁻¹ and 5.54 ng·ml⁻¹, respectively; median tmax for ropinirole with and without theophylline: 2.0 h and 1.5 h, respectively).

Conclusion: These results suggest a lack of significant pharmacokinetic interaction between the two drugs at current therapeutic doses.

Key words Drug interaction · CYP1A2 · Ropinirole

Introduction

Ropinirole is a novel, orally active dopamine D2-receptor agonist that has recently been marketed for the treatment of Parkinson’s disease (PD; Adler et al. 1997; Brooks et al. 1995; Rascol et al. 1996; Rascol et al. 1998). In vitro enzymology data show that the cytochrome P450 1A2 (CYP1A2) isoenzyme is mainly responsible for the oxidative metabolism of ropinirole (Bloomer et al. 1997). Theophylline is also a substrate for CYP1A2 (Ha et al. 1995; Rasmussen et al. 1995). There is therefore a risk, in vivo, that ropinirole could potentially interact with other drugs using the same metabolic pathway.

The aim of the present study was to investigate this potential drug-drug interaction, assessing the effects of ropinirole at steady state on the pharmacokinetics of a single intravenous (i.v.) dose of theophylline, and the effects of steady-state oral theophylline on the steady-state pharmacokinetics of ropinirole in patients with PD. A preliminary communication of this work has been previously presented [Taylor et al. 1997].
Methods

Patients

Twelve patients (ten males and two females) suffering from mild (Hoehn and Yahr stages 1–II.5; Hoehn and Yahr 1967) idiopathic PD, diagnosed according to the UK brain bank criteria (Gibb and Lees 1988), participated in this open study. The mean age of the patients with (SEM) was 59 years (8 years) and the mean duration of PD was 4 years (1 year). All patients participating in the study had been referred to the Toulouse University Hospital for treatment adjustment and, in all cases, the prescription of a dopamine agonist, such as ropinirole, was indicated to improve the patients’ symptomatic motor status.

All but one of the patients were being treated with l-dopa [mean dose 575 (79) mg day⁻¹], which could be combined with selegiline (n = 2, 10 mg day⁻¹) or trihexyphenidyle (n = 3, 10 (3) mg day⁻¹). Other concomitant non-parkinsonian medications were: hylopidaemic agents (n = 3), antihypertensive agents (n = 3), psychotropic drugs (n = 4) and digestive drugs (n = 1). None of these drugs were known to involve CYP1A2 as a significant metabolic pathway.

Antiparkinsonian and concomitant drugs had to remain stable for at least 4 weeks before patients could enter the study, and during the trial. Medical history, a physical examination, clinical laboratory tests (including standard haematology, liver and renal function assessments and the usual clinical chemistry tests) and an electrocardiogram (ECG) were normal in every patient at the beginning of the study. The study protocol was approved by the Toulouse 1 ethics committee and conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice Guidelines. All patients provided written informed consent and received a financial indemnity for participating in the study. All patients were given the option of continuing treatment with ropinirole in a compassionate protocol at the end of the present study.

Design

The study was conducted at the Toulouse Clinical Investigation Centre.

Ropinirole-theophylline interaction

Patients initially received a single 30-min intravenous (i.v.) infusion of theophylline (aminophylline, 5 mg·kg⁻¹ in 250 ml normal saline) on the first day (D0) as in-patients. Ropinirole was then introduced on D1 and up-titrated from 0.5 to 2.0 mg three times daily (t.i.d.) over a 4-week period, during which time patients were followed up as out-patients. A daily dose of 6 mg of ropinirole is known to be effective and superior to placebo as an adjunct to l-dopa in patients with mild PD (Rascol et al. 1996). When patients had reached steady state for ropinirole, they were rechallenged on D27 with a second i.v. dose of aminophylline to test the effect of ropinirole treatment on the pharmacokinetics of theophylline. Blood samples for determination of theophylline pharmacokinetics were collected during the theophylline i.v. challenges on D0 and D27, before and 15, 30 and 35 min, and 1, 1.5, 2, 3, 4, 6, 8 h and 12 h after the start of each infusion.

Theophylline-ropinirole interaction

When the first part of the study was complete, ropinirole (2 mg t.i.d.) was maintained at that dose from D28 to D47. During this period, oral controlled-release theophylline was up-titrated to reach a plasma concentration within the therapeutic range of 8–15 g·ml⁻¹. The maximal daily dose allowed for theophylline was 300 mg b.i.d. Theophylline plasma concentrations were monitored on D31, D35 and D38, immediately before the morning dose of theophylline, so that the daily drug dose could be adjusted to reach the desired plasma concentration. When such concentrations were reached, co-treatment with stable doses of oral ropinirole and theophylline were continued up to D40. Theophylline treatment was then stopped and ropinirole was continued alone for 7 more days (D41 to D47). Plasma samples (5 ml) for measuring ropinirole concentration were collected before and 0.5, 1, 1.5, 2, 3, 4 h and 6 h after morning administration of the drug on three occasions: D26 (steady-state ropinirole treatment before oral theophylline), D40 (with oral theophylline and D47 (after discontinuation of oral theophylline). Plasma samples (5 ml) for measuring theophylline concentration were also collected before and 0.5, 1, 1.5, 2, 3, 4, 6, 8 h and 12 h after the morning oral administration of ropinirole and theophylline on D40, to check that steady state had actually been reached.

Blood, collected in heparinized tubes (5 ml) for the measurement of plasma ropinirole and theophylline concentrations, was chilled, then centrifuged within 1 h of collection at 1500 g for 10 min at approximately 4 °C. Samples were frozen immediately in dry ice and stored at −80 °C. Samples for ropinirole assay were sent to Phoenix International Life Sciences, Saint-Laurent (Montreal), Quebec, Canada, whereas those for theophylline were sent to Pharmaco International, Richmond, Va., USA.

Plasma ropinirole concentrations were measured by radioimmunoassay. The lower limit of quantification was 0.08 ng·ml⁻¹ for a 0.1-ml sample. The recovery and coefficients of variation were less than 15% of the actual concentrations in quality-control samples. Plasma theophylline was quantified by an independent laboratory (Pharmaco International, Richmond, Va., USA) using a validated method involving high-performance liquid chromatography with ultraviolet detection. The lower limit of quantification was 0.05 g·ml⁻¹ for a 0.5-ml sample. The assay was validated and coefficients of variation were less than 15% of the actual concentrations in quality-control samples.

All antiparkinsonian drugs and concomitant medications were allowed throughout the study. On the pharmacokinetic profiling days, the patients were dosed in the fasted state. A standard breakfast and a standard lunch were served at 2.5 h and 5 h after dosing, respectively. Beverages containing caffeine (coffee, tea, cola) were not allowed on the pharmacokinetic profiling days. Alcohol and grapefruit juice were not allowed throughout the study.

Adverse events were assessed by spontaneous report and questioning every week during the dosing schedule, and on pharmacokinetic profiling days. Heart rate, blood pressure and a 12-lead ECG were recorded on D0, 1, 26, 27, 28, 31, 32, 35, 36, 38, 40 and 47. Additional ECGs were also obtained immediately before and at the end of the theophylline infusion (D0, D27), before, and 2 h and 12 h after the first ropinirole dose (D40), and before, and 2 h and 8 h after the first ropinirole dose (D26 and D47).

Pharmacokinetic analysis

Plasma concentration-time data for ropinirole and theophylline were analysed by non-compartmental methods using SmithKline Beecham in-house computer software that incorporates standard algorithms. Maximum plasma concentrations (Cmax) and the time to maximum concentrations (tmax) were derived by visual inspection of data from individual patients. The area under the plasma concentration-time curve (AUC0–t) for each drug was calculated by log-linear trapezoidal methods, and the terminal phase rate constant (z) for theophylline was calculated by log-linear trapezoidal methods, and the terminal phase rate constant (z) for theophylline was calculated by log-linear trapezoidal methods, and the terminal phase rate constant (z) for theophylline was calculated by log-linear trapezoidal methods, and the terminal phase rate constant (z) for theophylline was calculated by log-linear trapezoidal methods.